Comparison of 8-mm and 10-mm Diameter Fully-Covered Self-Expandable Metal Stents: A Multicenter Prospective Study in Patients with Distal Malignant Biliary Obstruction

Running title: FCSEMS for Distal Biliary Obstruction

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Abstract

Objectives: The time to recurrent biliary obstruction (TRBO) of unresectable distal malignant biliary obstruction is generally thought to be longer when a self-expandable metal stent (SEMS) with a thicker inner diameter is used for drainage, but the dependence on the inner diameter using a fully covered SEMS (FCSEMS) is uncertain. The objective of this multicenter prospective study was to compare TRBO and adverse events, such as cholecystitis and pancreatitis, in treatment of patients with unresectable malignant biliary obstruction using 8-mm and 10-mm diameter FCSEMS.

Methods: Eighteen tertiary-care centers participated in the study. Patients were allocated to the 8-mm and 10-mm diameter groups. TRBO, non-inferiority of the 8-mm FCSEMS, overall survival time, frequency and type of adverse events, and non-recurrent biliary obstruction (RBO) rate at the time of death were compared between the two groups.

Results: Median TRBOs did not differ significantly between the 8-mm (n=102) and 10-mm (n=100) groups (275 vs. 293 days, *P*=0.971). The hazard ratio of the 8-mm to 10-mm groups was 0.90 (80% confidence interval 0.77-1.04, upper limit lower than the acceptable hazard ratio (1.33) of the null hypothesis). Based on these findings, the

8-mm diameter stent was determined to be non-inferior to the 10-mm diameter stent. Survival time, incidence of adverse events, and non-RBO rate at the time of death did not differ significantly between the two groups.

Conclusions: TRBO with an 8-mm diameter FCSEMS was non-inferior to that with a 10-mm diameter FCSEMS. This finding is important for development of future SEMS. (UMIN 000013560)

Key words: Drainage, ERCP, Stents

Introduction

Endoscopic stent placement in patients with unresectable malignant distal biliary obstruction (MBO) improves obstructive jaundice and quality of life, and enables treatment such as chemotherapy [1-13]. Compared with plastic stents, several studies have reported high patency rates for self-expandable metal stents (SEMSs) [6-8]. Many prospective studies of partially covered SEMS (PCSEMS), in which both ends are uncovered, and uncovered SEMS (UCSEMS) have also been reported [10-13]. In patients treated with SEMS with flare to prevent migration [14], the time to recurrent biliary obstruction (RBO) is significantly longer in those treated with PCSEMS than in those treated with UCSEMS [15]. However, the general survival time has been extended by advances in treatment, such as chemotherapy [16-19], and patients requiring stent replacement as a reintervention have increased.

Fully covered SEMS (FCSEMS) have advantages of simple removal, which facilitates reintervention. The absence of a difference in time to RBO (TRBO) between FCSEMS and PCSEMS using a WallFlex Biliary RX^{TM} stent (Boston Scientific, Natick, MA) has been reported [20], and this stent has recently been widely used. A comparison of 6- and 10-mm diameter UCSEMS showed that TRBO was significantly longer in patients treated with a 10-mm diameter stent [21], but no prospective controlled study of the

effect of the FCSEMS inner diameter has been reported. It is thought that TRBO may be longer in cases with a FCSEMS with a large inner diameter, but there is no clear evidence for this position. Furthermore, in actual clinical practice, there seems to be no difference in TRBO between FCSEMS using 8- and 10-mm diameter stents, and a higher frequency of adverse events, such as cholecystitis and pancreatitis, is likely using a thick FCSEMS.

To investigate the potential non-inferiority an 8-mm diameter FCSEMS to a 10-mm diameter FCSEMS with regard to TRBO and the frequency of adverse events, we designed a multicenter prospective controlled study using a WallFlex Biliary RX^{TM} Fully Covered Stent, which has flare to prevent migration and is reported to have a relatively weak axial force [14, 15, 20]. The primary endpoint of the study was the TRBO of the 10-mm vs. 8-mm diameter FCSEMSs. The secondary endpoints were overall survival time, frequency and type of adverse events, and non-RBO rate at the time of death.

Methods

Patients

This study was a prospective multicenter randomized trial conducted at 18 tertiary-care centers. The study was approved by the Institutional Review Boards of each of the participating centers and performed according to the guidelines described in the Helsinki Declaration for biomedical research involving human subjects (Clinical trial registration number: UMIN 000013560).

Eligibility criteria

The inclusion criteria were (i) unresectable malignant distal biliary obstruction (≥2cm distal to the biliary hilum), (ii) definite clinical diagnosis of malignancy, such as metastasis, or definite pathological diagnosis of malignancy, (iii) written consent voluntarily given by the patient after a sufficient explanation was given to allow understanding of participation in the study, and (iv) age ≥20 years old at the time of giving consent. The exclusion criteria were (i) Eastern Cooperative Oncology Group performance status of 4, (ii) severe dysfunction in other organs (American Society of Anesthesiologist physical status grade III or IV), (iii) life expectancy ≤3 months, (iv) severe mental disorder, and (v) being estimated to be ineligible by the investigator.

In a comparison of PCSEMS and UCSEMS (both 10-mm diameter) for distal malignant biliary obstruction performed in Japan, the median duration of patency of PCSEMS was 187 days [15]. Based on this result, when the non-inferiority margin was

set at a hazard ratio (HR) of 1.33 based on an expected median duration of patency of 6 months in the control 10-mm diameter FCSEMS group and test treatment 8-mm diameter FCSEMS group, an exploratory study was designed setting the registration period at 24 months, the follow-up period at 12 months, one-sided α=0.1, and power at 70%. The necessary number of patients was determined using the Schoenfeld-Richter method, as 91 patients per group and 182 patients in total [22]. Considering that about 10% of patients were likely to be ineligible, the target number of patients was set at 200.

Randomization

For the treatment group, patients were randomly allocated by the data center, using the following factors that were expected to be involved in the TRBO and incidence of adverse events, with a minimization method used for these factors to minimize biases: 1) primary disease (pancreatic carcinoma or other than pancreatic carcinoma), 2) presence or absence of gallbladder enlargement, 3) presence or absence of previous drainage, and 4) participating center. Only the data center were aware of the details of the randomization procedure. The investigators at the participating centers were not informed of this procedure.

Treatment before stent insertion

Endoscopic retrograde cholangiography was performed when biliary obstruction by

malignant tumor was suspected on imaging diagnosis by ultrasonography or computed tomography, and the length and position of the obstruction was confirmed. Endoscopic biliary drainage was performed as needed. In this step, endoscopic nasobiliary drainage was used or a plastic stent was placed, and a decision on resectability was made while treating jaundice, as a rule [23]. However, cases diagnosed as unresectable at this time point were enrolled in the study and placement of the allocated FCSEMS was permitted.

Stent insertion

FCSEMS was endoscopically inserted in the normal manner. When no dilatation of the main pancreatic duct due to duct stenosis was noted, endoscopic sphincterotomy was performed. An 8-mm or 10-mm WallFlex Biliary RX™ Fully Covered Stent was used as allocated. The stent extended at least 10 mm above the top of the stricture and approximately 5 mm into the duodenum.

Course observation

Blood test was collected for examination, including hematology and biochemistry on the day after stent insertion (to evaluate possible adverse events), at least once within 5 days to 4 weeks (confirmation of the effect of drainage), and within 8 weeks. If subjective symptoms were present, such as fever and abdominal pain, blood sampling and imaging were performed to examine possible RBO and cholecystitis.

Definitions and statistical analysis

TRBO was defined as the period between stent insertion and RBO. RBO was defined as redilatation of the intrahepatic bile duct accompanied by an increase in biliary enzymes, and when bile duct dilatation was confirmed by imaging, endoscopic or percutaneous intervention was urgently performed (excluding gallbladder drainage for cholecystitis). When a patient died without RBO or follow-up was discontinued without intervention, the case was calculated as censoring. A Kaplan-Meier curve of per protocol set (PPS), in which stent insertion was possible, was constructed. TRBO data were fit to a Cox proportional hazard model with the allocation adjustment factors (excluding the participating center) as strata and the treatment method as a covariate to estimate the HR of the 8-mm group to the 10-mm group, using an 80% confidence interval (CI) corresponding to a one-sided significance level of 10%. The Wald method was used for constitution of the CI, and an upper limit of the 80% CI of the hazard ratio not exceeding the acceptable HR (1.33) of the null hypothesis was judged to indicate non-inferiority. The survival time defined as the time from stent insertion to death and was estimated using Kaplan-Meier methods. Between-group comparison of TRBO and survival time were performed using the log-rank method. When the stent could not be inserted, the reason was recorded.

The incidence of adverse events was also analyzed in the PPS using a chi-square test or Fisher exact test, as needed. Adverse events in patients in whom stenting was not possible were recorded separately. Cholecystitis was defined as abdominal pain accompanied by a fever ≥38°C, with thickening of the gallbladder wall on abdominal ultrasonography and tenderness consistent with a tense gallbladder (regardless of the presence of drainage). Pancreatitis was defined as abdominal pain accompanied by an increase in the serum amylase level (≥3 times the normal level). These definitions are identical to the Tokyo criteria 2014 [24], and severity was also according to these criteria. Pain at the time of stent insertion was defined as a case with abdominal pain requiring analgesics that did not meet any of the above conditions. Details of other complications were also recorded.

The non-RBO rate at the time of death was defined as the rate of patients without RBO until death. Methods and concomitant treatment (e.g., chemotherapy) were not specified, but were recorded when performed. For continuous variables, such as age, a Mann-Whitney U-test was used. All statistical analyses were performed using SPSS 24.0 (SPSS, Chicago, IL) and $P<0.05$ was regarded as significant.

Results

Patient characteristics

The registration period was set as July 1, 2014 to June 30, 2016, but the target number of patients was not reached and the period was subsequently extended to January 31, 2017. The following one-year period was set as the observation period (until January 31, 2018). A total of 202 eligible patients were enrolled, with 102 and 100 patients allocated to the 10-mm and 8-mm groups, respectively. FCSEMS insertion was not possible in 4 of the 202 patients (all in the 10-mm group) (Figure 1), but the inner diameter of FCSEMS was not associated with any of these events. The PPS comprised of 98 and 100 patients in the 10-mm and 8-mm groups, respectively. There were no significant differences in patient background between the two groups (Table 1). An effect of drainage (reduction of biliary enzymes and/or reduction of the bile duct diameter on imaging) was acquired in all 198 patients (the PPS) in whom stent insertion was possible.

Time to recurrent biliary obstruction (TRBO)

The median TRBO was 293 days in the 10-mm group and 275 days in the 8-mm group, with no significant difference between the groups (P=0.971, log-rank test) (Figure 2). The HR of the 8-mm to 10-mm group in the Cox proportional hazard model was 0.90.

The 80% CI using the Wald method corresponding to a one-sided significance level of 10% was 0.77-1.04, in which the upper limit of the 80% CI was smaller than the acceptable HR (1.33) of the null hypothesis. Based on this, the 8-mm diameter FCSEMS was judged to be non-inferior to the 10-mm diameter FCSEMS with regard to TRBO.

Survival time

The median (range) follow-up period was 188 (12-965) days in the 10-mm group and 193 (8-708) days in the 8-mm group, with no significant difference between the groups (*P*=0.949). In the PPS, 160 of 198 patients (80 in the 10-mm group and 82 in the 8-mm group) died during the follow-up period (and 164 of the whole 202 patients died during follow-up). The median survival time was 191 days in the 10-mm group and 196 days in the 8-mm group, again without a significant difference (*P*=0.942, log-rank test, Figure 3).

Adverse events

Cholecystitis developed in 16 (8.1%) of the 198 patients, including 10 (10.2%) in the 10-mm group and 6 (6%) in the 8-mm group (*P*=0.278, Table 2). Cholecystitis developed within one week, suggesting a direct influence of stent placement, in 4 (4.1%) and 1 (1%) patients in the 10-mm and 8-mm groups, respectively, with no

significant difference between the groups (*P*=0.167). Cholecystitis was improved by conservative treatment in 4 patients, but percutaneous drainage was needed in 12 patients. The median onset period was 10.5 days after stent placement (range: 2-363 days, showing wide variation). Pancreatitis developed in 14 (7.1%) of 198 patients, including 4 (4.1%) in the 10-mm group and 10 (10%) in the 8-mm group. The difference was not significant (*P*=0.104, Table 2). Pancreatitis was severe in one patient with distal bile duct carcinoma in the 10-mm group and moderate in one patient with pancreatic carcinoma in the 8-mm group, but mild in the other 12 patients, and was conservatively improved in all patients. Pain at stent insertion occurred in 28 patients, including 17 (17.3%) in the 10-mm group and 11 (11%) in the 8-mm group, with no significant difference between the groups (P= 0.200, Table 2). Other adverse events included perforation during insertion in one patient in the 8-mm group and hemorrhage from a duodenal ulcer on the opposite side of the papilla in one patient in the 10-mm group.

Non-RBO rate at the time of death

The non-RBO rates at the time of death were 66.3% (53/80) in the 10-mm group and 63.4% (52/82) in the 8-mm group, with no significant difference between the groups (*P*=0.706).

Discussion

The usefulness of SEMS has been shown in a comparison with plastic stents since SEMS became available for MBO, and many controlled studies of types of SEMS have been performed. Isayama et al. noted that the definitions of TRBO and adverse events differ among these studies and proposed uniform definitions in the Tokyo criteria 2014 [24]. The present prospective study was initiated before publication of the Tokyo criteria 2014, but the definitions were the same. The incidence of RBO during the observation period, which was the outcome proposed in the Tokyo criteria 2014, but was not used as an endpoint of this study, was 77/198 patients (38.9%, median observation time: 190 (8-995) days), including 39/98 (39.8%) and 38/100 (38.0%) in the 10-mm and 8-mm groups, respectively, with no significant difference between the groups (P=0.795). The non-RBO rates at 3, 6, and 12 months using the Kaplan-Meier method were 85.3, 70.2, and 40.7%, respectively, in the 10-mm group and 89.6, 65.4, and 42.7%, respectively, in the 8-mm group.

FCSEMS, a stent with a larger inner diameter tends to be selected. Many previous studies comparing types of SEMS used 10-mm diameter SEMS, and the utility of a

12-mm diameter FCSEMS has also been reported [25]. Certainly, in the present study, there was no difference in the insertion success rate between 10-mm and 8-mm diameter FCSEMS and the thickness of the delivery shaft was also the same. The thinner 8-mm FCSEMS felt easier to insert in actual clinical practice. Non-inferiority of the 8-mm diameter FCSEMS to the 10-mm diameter FCSEMS in TRBO was demonstrated in the current study, suggesting that the direction of FCSEMS development should not be limited by the inner diameter. TRBO after FCSEMS insertion is also strongly influenced by migration, which is likely to occur more as the SEMS axial force increases [26]. The axial force of an 8-mm diameter WallFlex™ Fully Covered Biliary Stent may be smaller than that of the 10-mm diameter stent (measured values are unclear), and this may have contributed to the non-inferiority in TRBO.

Advance of a lesion to the cystic duct is a reported risk factor for cholecystitis, but definite diagnosis of this event is difficult without cholangiography. In the current study, patients with MBO accompanied by liver metastasis were enrolled and allocated to a group before cholangiography, and then FCSEMS insertion was directly permitted. Thus, the presence or absence of gallbladder enlargement was used as an adjustment factor in random allocation, instead of advance of the lesion to the cystic duct, because it was easier to diagnose. The incidences of cholecystitis were 10.2% (10/98) and 6%

(6/100) in patients with and without gallbladder enlargement, respectively, without a significant difference (*P*=0.278). Regarding pancreatitis, a lower incidence in the 8-mm group was expected, but no significant difference was found. Many patients with pancreatic cancer also have obstruction of the main pancreatic duct, resulting in dilatation of the duct on the caudal side, and the incidence of pancreatitis was significantly lower in these patients (primary disease: pancreatic carcinoma in 6/144 (4.2%) and other disease in 8/54 (14.8%) patients, *P*=0.009).

There are several limitations in this study. First, the duration of follow-up was ≤3 months in 47 (23.3%) of the 202 patients, but this was due to death in all cases (45 died of primary disease. Table 3). One reason for these outcomes may be inclusion of many elderly patients aged ≥80 years (44 patients) because an upper age limit was not specified in the inclusion criteria. Second, the cause of RBO was not identified. For FCSEMS, migration has attracted attention as a cause of RBO, but identification of the cause can be difficult in many cases because migration and sludge occur together or it is difficult to judge whether the cause is migration or tumor overgrowth. In this study, the cause was not investigated because standardization among many institutions was difficult.

In conclusion, a prospective randomized multicenter study using the WallFlex Biliary

RX™ Fully Covered Stent showed that an 8-mm diameter FCSEMS was not inferior to a 10-mm diameter FCSEMS for TRBO or the incidence of adverse events. These findings may be important in further development of SEMS.

COI

Authors declare no Conflict of Interests for this article

Potential competing interests: None.

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Figure Legend

Figure 1. Flowchart showing results of inclusion, randomization, reasons for failure of stent insertion and follow-up of patients.

FCSEMS, fully covered self-expandable metal stent, RBO, recurrent biliary obstruction

Figure 2. Kaplan-Meier curve showing time to recurrent biliary obstruction (per protocol set).

The hazard ratio (HR) of the 8-mm to 10-mm group in the Cox proportional hazard model was 0.90. The 80% CI using the Wald method corresponding to a one-sided significance level of 10% was 0.77-1.04, in which the upper limit of the 80% confidence interval was smaller than the acceptable HR (1.33) of the null hypothesis. Based on this, the 8-mm diameter fully covered self-expandable metal stent (FCSEMS) was judged to be non-inferior to the 10-mm diameter FCSEMS with regard to time to recurrent biliary obstruction.

Figure 3. Kaplan-Meier curve showing cumulative patient survival (per protocol set).

There was no significant difference in patients survival between 8-mm and 10-mm diameter fully covered self-expandable metal stent group (P = 0.942, log-rank test).

Table 1 Patients characteristics			
	FCSEMS		
	10mm (n = 102)	8mm (n = 100)	*P* value
Median age year (range)	74.0 (35 - 95)	74.0 (46 - 93)	0.400
Gender (%)			
male	56 (54.9)	56 (56.0)	0.875
female	46 (45.1)	44 (44.0)	
Primary disease (%)			
Pancreatic carcinoma	73 (71.6)	73 (73.0)	0.820
Ohers	29 (28.4)	27 (27.0)	
cholangiocarcinoma	8 (7.8)	14 (14.0)	
GB carcinoma	3 (2.9)	6 (6.0)	
metastatic lymph node	11 (10.8)	6 (6.0)	
ampulla carcinoma	4 (3.9)	0 (0.0)	
unknown	3 (2.9)	1 (1.0)	
Previous GB swelling (%)			
presence	51 (50.0)	50 (50.0)	1.000
absence	51 (50.0)	50 (50.0)	
Previous drainage (%)			
presence	60 (58.8)	59 (59.0)	0.980
absence	42 (41.2)	41 (41.0)	
Total bilirubin mg/dl, median (range)			
Before stent deployment	2.40 (0.3 - 26.8)	2.10 (0.3 - 25.0)	0.347
5 days~4 weeks after stent deployment	1.40 (0.2 - 24.7)	1.10 (0.3 - 11.3)	0.089
Chemo (radio) therapy (%)			
with	57 (55.9)	64 (64.0)	0.239
without	45 (44.1)	36 (36.0)	

FCSEMS: Fully-covered self-expandable metal stents

GB: Gallbladder

Table 2 Cholangiography findings, adverse events and patients' follow-up			
	FCSEMS		
	10mm (n=98)	8mm (n=100)	*P* value
Length of FCSEMS (%)			
6cm	23 (23.5)	24 (24.0)	1.00
8cm	75 (76.5)	76 (76.0)	
Length of biliary stricture			
median (range)	21.0 (10-42)	21.5 (8-41)	0.777
Maximum diameter of proximal bile duct			
median (range)	12 (8-20)	12 (9-20)	0.794
Cholecystitis (%)			
occurred (all)	10 (10.2)	6 (6.0)	0.278
within 7 days	4 (4.1)	1 (1.0)	0.167
not occurred	88 (89.8)	94 (94.0)	
Pancreatitis (%)			
occurred	4 (4.1)	10 (10.0)	0.104
not occurred	94 (95.9)	90 (90.0)	
Abdominal pain when stent insertion (%)			
with	17 (17.3)	11 (11.0)	0.200
without	81 (82.7)	89 (89.0)	
Chemo (radio) therapy (%)			
with	56 (57,1)	64 (64.0)	0.323
without	42 (42.9)	36 (36.0)	
Recurrent biliary obstruction rate until patients die (%)			
occurred	27 (33.8)	30 (36.6)	0.706
not occurred	53 (66.3)	52 (63.4)	
Observation period			
days median (range)	188 (12-965)	193 (8-708)	0.949

FCSEMS: Fully-covered self-expandable metal stents

Table 3 Patients' characteristics (death within 3 months)			
	FCSEMS		
	10mm (n = 24)	8mm (n = 23)	*P* value
Median age year (range)	74.5 (45 - 95)	78.0 (64 - 93)	0.192
Gender (%)			
male	17 (70.8)	13 (56.5)	0.307
female	7 (29.2)	10 (43.5)	
Primary disease (%)			
Pancreatic carcinoma	16 (66.7)	17 (73.9)	0.587
Others	8 (33.3)	6 (26.1)	
cholangiocarcinoma	0 (0.0)	1 (4.3)	
GB carcinoma	1 (4.2)	2 (8.7)	
metastatic lymph node	4 (16.7)	2 (8.7)	
ampulla carcinoma	1 (4.2)	0 (0.0)	
unknown	2 (8.3)	1 (4.3)	
Previous drainage (%)			
presence	10 (41.7)	12 (52.2)	0.471
absence	14 (58.3)	11 (47.8)	
Cholecystitis (%)			
occurred	2 (8.3)	1 (4.3)	1.00
not occurred	22 (91.7)	22 (95.7)	
Pancreatitis (%)			
occurred	2 (8.3)	1 (4.3)	1.00
not occurred	22 (91.7)	22 (95.7)	
Total bilirubin mg/dl, median (range)			
Before stent deployment	3.45 (0.6 - 17.6)	2.90 (0.4 - 25.0)	0.876
5 days~4 weeks after stent deployment	1.40 (0.7 - 16.1)	1.10 (0.3 - 11.3)	0.473
Chemo (radio) therapy (%)			
with	10 (41.7)	9 (39.1)	0.239
without	14 (58.3)	14 (60.9)	
Recurrent biliary obstruction until patients die (%)			
occurred	5 (20.8)	2 (8.7)	0.243
not occurred	19 (79.2)	21 (91.3)	

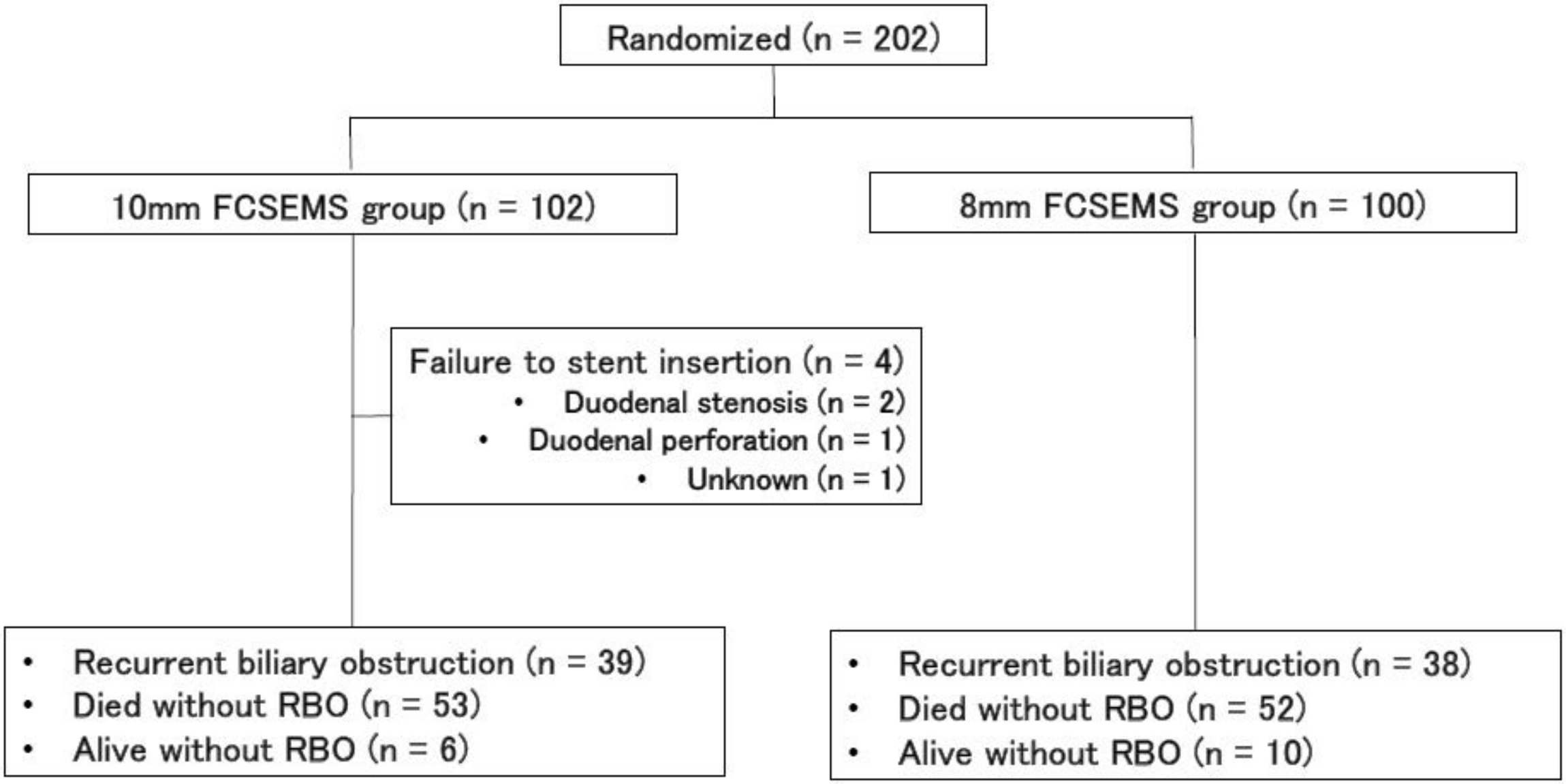
Cause of death			
Primary disease	23 (95.8)	22 (95.7)	1.00
Others	1* (4.2)	1** (4.3)	
Observation period			
days median (range)	47 (12-87)	66 (8 - 87)	0.19

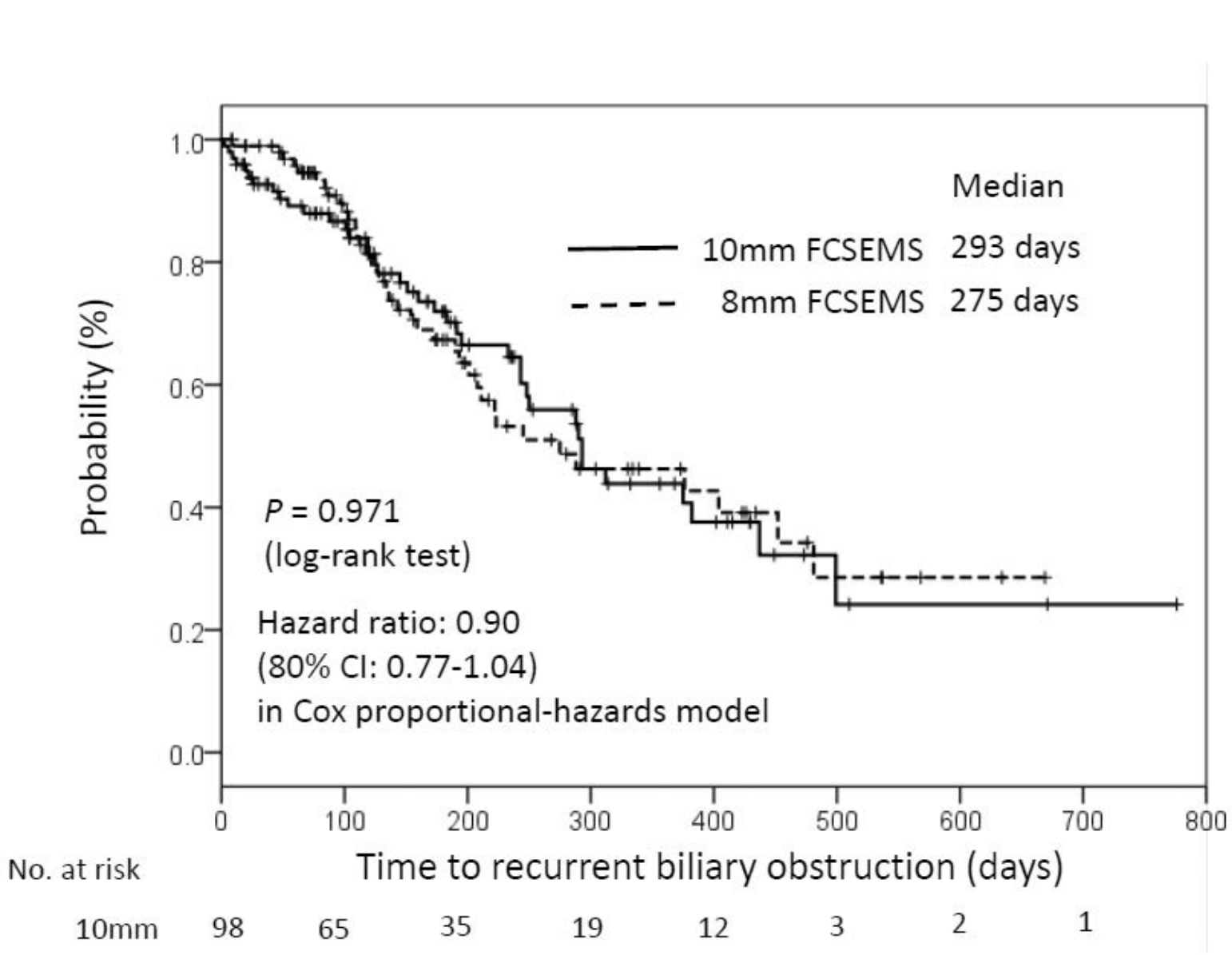
FCSEMS: Fully-covered self-expandable metal stents

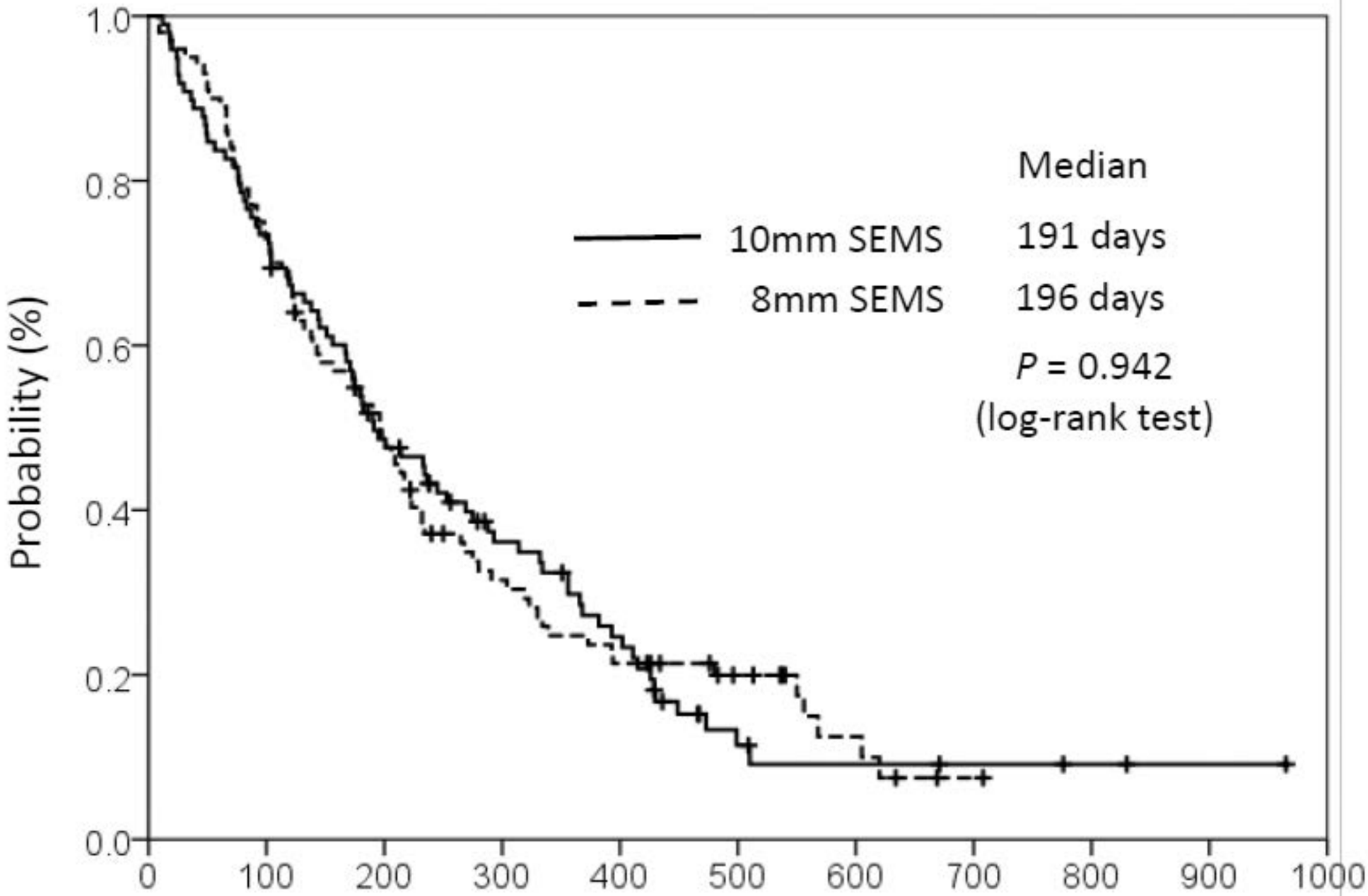
GB: Gallbladder

*: sudden death due to ventricular fibrillation on day 77

**: death due to aspiration pneumonia on day 41


Randomized (n = 202)
10mm FCSEMS group (n = 102)
8mm FCSEMS group (n = 100)
Failure to stent insertion (n = 4)
• Duodenal stenosis (n = 2)
• Duodenal perforation (n = 1)
• Unknown (n = 1)
• Recurrent biliary obstruction (n = 39)
• Died without RBO (n = 53)
• Alive without RBO (n = 6)
• Recurrent biliary obstruction (n = 38)
• Died without RBO (n = 52)
• Alive without RBO (n = 10)


Median
10mm FCSEMS 293 days
8mm FCSEMS 275 days
P = 0.971
(log-rank test)
Hazard ratio: 0.90
(80% CI: 0.77-1.04)
in Cox proportional-hazards model
Probability (%)
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
700
800
Time to recurrent biliary obstruction (days)
No. at risk
10mm 98 65 35 19 12 3 2 1
8mm 102 67 32 18 12 5 2 0



No. at risk

10mm	98	72	46	29	19	6	4	3	2	1
8mm	102	67	47	28	19	12	5	1	0	